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Biochemistry of Drugs Action and their Resistance Mechanism: A Brief Discussion

Shazia Anwer Bukhari[1], Anam Tariq[1], Asim Rehman[1], Ayesha Saeed[1], Chanda Javed[1], Haroon Amin[1], Muhammad Jahangeer*[1], Muhammad Bilal[1], Qurat-ul-ain Babar[1], Rafay ur Rehman Cheema[1], Rawaba Arif[1], Shoukat Hussain[1]

[1]Department of Biochemistry, Government College University Faisalabad, Pakistan, 38000.

*Corresponding email: rajahangeer@gcuf.edu.pk

Abstract

Pharmaceutical drug is a chemical substance which is used to maintain growth, cure, treat, prevent and diagnose a disease. Up to the middle of the nineteenth century, man had access to a wide range of natural remedies to ease his suffering. As part of pharmacodynamics, we consider both drug activity and drug effect, which refers to the first effects of therapeutic receptor contact and the effects that follow. Infections are a leading cause of mortality in the underdeveloped nations. This is primarily owing to the advent of emerging infectious agents, more particularly the emergence of antibiotic resistance. Drug resistance or Antimicrobial resistance (AMR), progresses when microbes, including parasites i.e viruses, bacteria and fungi no longer effective against a drug that formerly treated them effectually. Clinicians will benefit from a better grasp of the processes of antibiotic resistance when it comes to prescribing antibiotic. As a result of this review, researchers are encouraged to apply gene manipulation, increased usage of stem cells (adult and embryonic), and improve bioavailability of nutrients utilizing nanotechnology in order to overcome the negative effects of pharmaceutical medications.

Keywords: Pharmaceutical drug, Pharmacodynamic, Anticonvulsant medicines, Anti-cancer drugs, Antipyretic Drugs, Personalized Medicines, Anti-aging drugs.

I. Introduction

A pharmaceutical drug is a chemical compound that binds to proteins in the body to trigger a biological process. This is the basic principle underlying most medication. As these chemicals enter the systemic circulation, they associate with specific proteins, significantly alter the cell's functioning. A medication is a chemical substance with a known structure that, when introduced to a biological system, shows physiological effect (Everett, 2015). A medicinal drug, also known as a pharmaceutical drug, is a chemical substance which is used to maintain growth, cure, treat, prevent and diagnose a disease. Pharmaceutical medicines are also divided into classes of medicinal products— groups of related medicinal products that have identical chemical structures, a single mechanism of action, a correlated method of action that is used for the same disease (binding to the same biological objective). The natural medicines were all available to alleviate the pain and misery of man up until the middle of the nineteenth century. Chloral hydrate, 1st synthetic drug, was formulated in 1869 and launched in some countries as a sedative hypnotic drug. Spin-offs from synthetic colorings and

textiles were the first pharmaceutical firms and are very responsible for the rich supply of organic substances resulting from coal distillation (coal-tar).

Pharmacodynamics includes the physiological and biochemical drugs effects and their mechanisms of action within or on the body of parasites and micro-organisms. It takes into account drug activity referring to the initial effects of the interaction between therapeutic receptors and the drug effect referring to the effects afterwards (He et al., 2015). Medication treatment aims to produce the desired severity and length of a specific pharmacological response while preventing adverse drug-reactions. An agonist is a receptor-binding drug, which changes (stabilizes) the percentage of receptors in active conformation and induces a biological reaction. Physiological antagonism occurs when two receptors and pathways work against each other on the same physiological system. A medication that suppresses the effect of a second drug by decreasing its absorption, adjusting its delivery or increasing its rate of removal induced pharmacokinetic antagonism.

A number of neurotransmitter receptors modulate opening and closing of ion channels through voltage gating or ligands. An example of a ligand-gated receptor is the nicotinic acetylcholine receptor. The G- protein couple receptor involved when the extracellular ligand binds to the receptor activate an intracellular GTP- (protein which helps in binding), which regulate an enzyme which produce an intracellular second messenger. The receptors of protein tyrosine kinase are normally transmembrane enzymes that only contain phosphorylate residues of tyrosine, not threonine and serine residues. The hormones that control the production of the gene in the nucleus are lipophilic and freely divert to the receptor through the cell membrane. The glucocorticoids are mostly inactive in the cytoplasm until they bind to the steroid glucocorticoid ligand. Intracellular receptors likely sulfonamides, penicillins, fluorochinolones, aminoglycosides, trimethoprim, macrolides and phenicols are also important to mediate the function of antimicrobic drugs. Action mechanisms include bacterial protein syntheses, cell wall synthesis inhibitors, inhibition of enzymatic activity, and cell membrane permeability alteration (Forrester et al., 2018).

An association between two or more drugs that makes the overall effect of each drug greater than the amount of each drug's individual effects is called drug synergism. A synergistic effect may be advantageous or negative. In treating a person case and discouraging the creation of resistance combination therapy with two or more antibacterial drugs can be useful (Palmer & Sorger, 2017). Types of synergism are additive (summation) and supra-additive (Potentiation). Summation involves when two medicines are given in a biological system together, the final effect is identical to the algebraic number of their size. In Supra-additive, the end result is much more than the mere algebraic sum of the magnitude of individual medicines when two medications are taken together. This review highlights the importance of pharmaceutical drugs to combat different diseases and encourage researchers to more explore the medicinal properties of different drugs.

II. Anticonvulsants drugs

Anticonvulsants are commonly called anti-seizure or antiepileptic drugs are the diverse groups of pharmacologic drugs mainly used in treatment of epilepsy and are also used in treatment of personality disorders so these act as mood stabiliser and also used for neuropathic pain treatment. Anti-seizure drugs basically suppress unnecessary firing of

nerve cells during epileptic conditions. Anticonvulsant drugs may block the sodium channels and also increase gamma aminobutyric acid (GABA) activity (Suleria et al., 2017). In the worldwide the epilepsy is controlled, but it is not cured by using the medicines so surgery may be recommended in many cases. Actually, epilepsy is not considered as single type disorder it is a group of diseases with vastly symptoms other target of anticonvulsant drugs are including the voltage gated calcium channels. So, by blocking of Na and Ca channels, anticonvulsant drugs may decrease the release of glutamate. Minimum data is available to understand the specific action of these drugs because optimum or good selection of therapy, inadequate knowledge of persons/ patient's genetic information. Moreover, formation of new and novel anticonvulsant drugs and their research regarding their mechanism and actions of recognized drugs, are continuous increase the complexity level in spectrum of their targets related for therapy (Kuzmanova & Stefanova, 2017).

2.1 Mechanism of actions

Anticonvulsant drugs mechanism of action is not fully understood but these drugs will help to control the warning sign of epilepsy. Actually the anticonvulsant drugs act basically the following important mechanisms firstly these drugs modulate the voltage gated ions (Na and Ca) channels and these drugs may also enhance the GABA activities so these help to inhibit the excitation of neurons (Kuzmanova & Stefanova, 2017).

2.1.1 Calcium channels

These voltage ion channels are similar to the sodium channels and alpha subunit of calcium channel is the homologue of alpha 1- subunit of sodium channel and it form the calcium channels pores. According to the potential of membrane mainly the calcium channels are classified in to high and low threshold. Low threshold T type calcium channels are predominantly expressed in thalamocortical relay of neurons and believed in generation of 3- spike and wave discharge and it is mainly characteristics of generalized seizures. But the high threshold calcium channels are classified by pharmacological characters into L, N, P, Q and R types and these channels are distributed neurons system on dendrites and nerve terminals (Deshmukh et al., 2011).

2.1.2 Sodium channels

Sodium channels have multi units' structures and forms sodium selective gated pores through the cell membrane. A- Subunit is the important component of sodium channels. But in mammalian brain cells, alpha subunits associated with 2 subunits such as beta 1 and beta 2. In the normal potential, the sodium channels present in the closed state but in depolarization state, sodium channels are activating and facilitate the ion flux. Thereafter, sodium channels are enters in the inactivated state and repolarization of neuron membrane converts channels back to lasting state, from which it responds to depolarization (Lee et al., 2009).

2.2 Gamma- aminobutyric acid (GABA) action

It is the main inhibition neurotransmitter in mammalian brain nervous system. GABA plays role in controlling the glutamate mediated excitation activities with in cortex. There are 2 major subtypes of GABA receptors, the GABA-A and GABA-B and a new GABA-C. GABA-A receptors are present on postsynaptic membranes and these are participated in neurotransmission (Maljevic et al. 2019).

Actually GABA-A receptor is the part of gated ion channels which consists of 5 membrane subunits and form pores through which the Cl ions enters in postsynaptic neurons. These 5 subunits consist of 4 distinct transmembrane domains. And subunits form ionophore have designated α, β, -γ, δ and ρ and each with exception the δ, having

multiple isoforms, and have the 6 a subunits (α_1-α_6), 4 β subunits ((β_1~β_4), 3 *y* subunits (γ_1-γ_3), a δ subunit and 2 ρ sub-units (ρ_1-ρ_2), appearing to be localized in the retina (Deshmukh et al., 2011).

III. Antipyretic Drugs

Typical temperature of body is somewhere in the range of 36.0 and 37.5°C, with intraindividual inconstancy of 0.5–1.0°C relying upon the hour of day. Raised internal heat level is named pyrexia or hyperthermia (Balli & Sharan, 2020). Pyrexia, additionally alluded to as fever, is a versatile reaction to a physiologic pressure that is firmly managed through endogenous pyrogenic and against pyretic pathways, and is related with an increment in the hypothalamic set point. The basic "endogenous pyrogens" engaged with delivering a profoundly managed provocative reaction to tissue injury and diseases are polypeptide cytokines. Cytokines responsible for fever, for example, IL-1β, TNF and IL-6, are those that act openly on the nerve center to influence a temperature reaction (Li et al., 2020). Exogenous pyrogens, like microbial surface segments, inspire pyrexia most regularly through the incitement of pyrogenic cytokines. The gram -ve bacterial external film lipopolysaccharide (endotoxin), be that as it may, is fit for working at the level of the nerve centre, similarly as IL-1.

PGE2 is accepted to be the proximal facilitator of the febrile reaction. Preoptic neurons bearing E-prostanoid receptors change their inborn terminating rate because of PGE2, inspiring a rise in the thermoregulatory control system (Salehzadeh et al., 2020). PGE2 have four cellular receptors: EP1 through EP4 (Przybyła et al., 2021). The receptor subtype took part in pyrogenesis still unknown. Although mice lacking the neuronal PGE2 receptor subtype EP3 reveal an impaired febrile response to both endogenous pyrogens and exogenous (endotoxin), studies in rats appear to involve the EP4 receptor.

Fever is firmly controlled by the insusceptible reaction. Provocative improvements setting off the age of propyretic messages incite the arrival of endogenous antipyretic substances. Substances like arginine vasopressin (AVP), a-melanocyte animating chemical, and glucocorticoids act both halfway and incidentally to restrict pyrexia (Lee & Simmons, 2018).

3.1 Mechanism of Action

Cyclooxygenase (COX) is the chemical that changes ARA into the pioneers of prostaglandins. COX has 2 isoforms: COX-1 and COX-2. COX-1 is basically communicated in non-inflammatory cells, though COX-2 is communicated in initiated lymphocytes, polymorphonuclear cells, and other incendiary cells. Ibuprofen and non-selective NSAIDs hinder both COX isoforms and in this manner decline prostaglandin and thromboxane blend all through the body. Arrival of prostaglandins essential for homeostatic capacity is disturbed, as is arrival of prostaglandins engaged with irritation (Osafo et al., 2017).

The COX-2-specific inhibitors have less impact on the prostaglandins engaged with homeostatic capacity, especially those in the gastrointestinal plot. The significant distinction between the systems of activity of anti-inflammatory medicine and different NSAIDs is that ibuprofen acetylates and subsequently irreversibly restrains COX, though the hindrance delivered by different NSAIDs is reversible. The irreversible activity of acetylsalicyclic acid brings about a more drawn out span of its antiplatelet impact and is the reason for its utilization as an antiplatelet drug (Janarthanan & Adalarasan, 2019).

VI. Anti-stress Drugs

Depression is a genuine psychological instability; however, it may be successfully treated with accessible medicine. Supplies of specifically accessible antidepressants can be utilized to securely treat depression with no harmful reaction (Leonard, 2018). There are no imaging anomalies or biomarkers helpful in deciding the pathophysiology of wretchedness over a long period. Study on brain autopsy uncovers no settled primary or neurochemical anomalies. Most of the accessible medications have been tentatively found. A large portion of the current speculations depend on the "amine theory". The above all speculation of disposition unsettling influence identifies with changes in biosynthetic level. It is accounted for that downturn is brought about by practical disability catecholamines, especially norepinephrine (NE), though madness is brought about by a useful abundance of catecholamines at the basic neural connections in the mind. The beginning of stress has been discovered to be identified with changes in degrees of essential amines in the mind, for example, NE, epinephrine, dopamine, , serotonin, indolamine, 2 catecholamines & 5-hydroxytryptamine (Yuan et al., 2015).

4.1 Antidepressants and their classification

In 1958, Tofranil, an antidepressant, was found which was categorized as:

1. Monoamine oxidase inhibitors (MAOI's)
2. Tricyclic antidepressants (TCA's)
3. Non-TCA antidepressants.
4. Serotonin-norepinephrine reuptake inhibitor (SNRI)
5. Selective serotonin-reuptake inhibitors (SSRI's)

The TCAs repress both serotonin (5HT) and norepinephrine (NE). This wonder being the important component of actions of antidepressants alters the physiological behavior of neuro-receptors. TCAs hinder muscarinic, histaminic receptors & α1 adrenergic. Although, these particles may prompt event of various results in patients (Wongrakpanich et al., 2018).

4.2 Monoamine oxidase inhibitors (MAOIs)

MAOIs remained the principal types of drugs responsible to treat depression. They are convincing, but they have generally been replaced by antidepressants which are safer and cause fewer reactions (Williams et al., 2018). In specific cases, they ease stress when different medicines have fizzled. Antidepressants, for example, MAOIs ease sorrow by influencing synthetic couriers (synapses) utilized to convey between synapses (Suchting et al., 2021).

Just like other medications for depression, MAOIs work by eventually affecting changes in the cerebrum that are effective in stress (Wongrakpanich et al., 2018). A protein known as monoamine oxidase is dedicated to clearing the norepinephrine, dopamine and serotonin synapses from the mind. MAOIs stop this from happening, making many of these synthetic mental compounds available to shock changes in both cells and circuits that have been affected by misery. MAOIs likewise influence many synapses in the mind and stomach related structure, initiating reactions (Yuan et al., 2015). MAOIs are occasionally utilized for the treatment of Parkinson's sickness. As a result of reactions and safety concerns, MAOIs are regularly used when different antidepressants show no significant effects (Suchting et al., 2021).

4.3 Tricyclic antidepressants

Tricyclic antidepressants contrast in their overall consequences for acetylcholine, serotonin & norepinephrine. The dissimilarities are imitated in the way TCAs are used and, most importantly, in their tendency to achieve certain results (Wongrakpanich et al., 2018). For example, amitriptyline (Elavil) causes dry mouth, blockage & more sedation

than other TCAs. Antidepressants expanded the danger of self-destructive reasoning and conduct in momentary examinations in kids and young people with wretchedness and other mental issues. Anybody considering the utilization of any anti-stress medication in a kid or young adult should offset this danger with the clinical need. Patients who are begun on treatment ought to be firmly noticed for clinical deteriorating, self-destructive reasoning or conduct, and unordinary changes in conduct (Yuan et al., 2015).

4.4 Non-TCA antidepressants

The main line of medicines responsible to treat depression is the non-TCAs which incorporates SSRIs. These specialists are relative more secure with better acceptability. Those patients which don't show any reaction to different medications or experiencing persistent pain or headache are given TCAs (Gong et al., 2019). Notwithstanding, the current reports propose that the optional amine TCAs (desipramine & nortriptyline) have more results than tertiary amine TCAs.

In this unique circumstance, the SSRIs and SNRIs are strong first line decisions. Benzodiazepines keep on seeking contention and, in essential consideration; their utilization ought to be restricted to short-term use as adjuvants to introductory pharmacological treatment. The TCAs and MAOIs show more harmfulness than the more up to date antidepressants, yet their viability in nervousness problems is certain (Roy-Byrne et al., 2008). Expert treatment alternatives incorporate benzodiazepines and different anticonvulsants just as the abnormal antipsychotics, either alone or as expanding specialists. There is a reassuringly powerful armamentarium of anxiolytic medications, however to improve consistence and treatment reactions, these specialists ought to be endorsed prudently after due thought of their individual pharmacological benefits and disservices drawbacks.

4.5 Serotonin-norepinephrine reuptake inhibitor (SNRI)

Serotonin and norepinephrine reuptake inhibitors (SNRIs) are a class of meds that are successful in treating stress (Gong et al., 2019). SNRIs are additionally in some cases used to treat different conditions, for example, nervousness problems and long haul (persistent) torment, particularly nerve torment. SNRIs might be useful when you have pain along with stress. NRIs relieves stress by influencing synthetic couriers (synapses) used to convey between synapses (Gong et al., 2019).

Just like medications that are responsible for treating depression, SNRIs act via affecting changes in cerebrum & communication in mind nerve cell known to direct mind-set, to help diminish anxiety. SNRIs block the reabsorption (reuptake) of the synapses norepinephrine and serotonin in the mind (Wongrakpanich et al., 2018). Results are typically gentle and disappear after the initial not many long stretches of treatment. Taking your prescription with food may diminish sickness. On the off chance that you can't endure one SNRI, you might have the option to endure an alternate one, as each SNRI shifts in substance buildup (Wongrakpanich et al., 2018).

4.6 Selective serotonin reuptake inhibitors (SSRIs)

The mostly recommended medicines to treat depression are SSRIs. They can alleviate signs of normal to severe pessimism, are generally protected, and generally have fewer reactions than the different kinds of antidepressants. SSRIs Treat discouragement by raising level of serotonin in the brain (Williams et al., 2018). Serotonin is an important synthetic carrier (synapses) that transfer signals among mind nerve cells (neurons). The reabsorption (reuptake) of serotonin is blocked by SRIs into neurons. This makes serotonin more available to advance the spread of messages between neurons. SSRIs are known as special because they mainly stimulate serotonin, not many synapses (Yuan et

al., 2015). SSRIs may be used to cure conditions other than wretchedness, for example, tension problems. It is referred to as abstinence syndrome (Wongrakpanich et al., 2018).

V. Anti-aging Drugs

Aging is a stage of life since the universe created. Human are passing through several stages of life from birth to death which includes childhood, youth and aging. Youth stage of life is a best part of life with respect to health. Aging had thought universal, integral and natural process. It has no major benefits except wisdom. If we draw the health on y-axis and the number of years on x-axis, it will produce a curve like triangle. The curve is called curve of life, which is tilted with its peak at 25-30 years (Piskovatska et al., 2019). Drug that inhibits aging assists to create it rectangle. Several normal aging processes often cause authentic disorders. It is determined that to combat an aging process may cause an enhancement of a disease related to age. Drug that inhibits aging is a developing branch of applied medicine and medical science. It treats the basic reasons of aging and goals at lessening any disease related to age (Klimova et al., 2018). Its aim is to rise the healthy lifetime of humans attain young features. Alternative and Predictable medicinal disciplines are utilized in a unified access to attain the best promising outcome for the patient.

Aging involved three biochemical processes. These are methylation, oxidation methylation and glycation. Different processes are hormonal deregulation and chronic inflammation.

5.1 Oxidation

Free radicals in minor and precise amounts are beneficial in normal breakdown. They play an important role in numerous normal mechanisms which occur in the body which include breathing. These free radicals are mostly formed during breakdown of oxygen inside the cells. The difficulty arises when the manufacturing of these free radicals rises and remain uncontrolled. It is possible to divide free radical processes into three distinct stages. Initiation, Propagation, and Termination are the three stages. Free radicals are deactivated inside the cells as soon as they are produced by the defense mechanism, which eliminates them by hunting out antioxidants and increases the elimination of material already damaged by free. If their want to place it in training, you need to avoid exposure to free radicals from smoking, pollution and poor diet (Homma & Fujii, 2015). As the name suggests, antioxidants are molecules that disrupt chains. Antioxidant is any substance that significantly slows or stops the oxidation of an oxidizable substrate when it is present in small amounts compared to that substrate. As a result, free radicals cause damage to the cell membrane, which is composed of lipid and protein. Glycation is another crucial aging process caused by their partnership, which produces the molecule malondialdehyde, which is extremely harmful.

5.2 Glycation

When protein attaches with molecules of glucose and other sugar i.e. fructose it is called glycation. This causes brownish discoloration of tissues. Cross-linking occurs when sugar attaches to a protein molecule. Advanced Glycation End products (AGEs) are formed when cross-linked proteins combine with free radicals and additional toxins to (AGEs). Special attachment sites named RAGEs connect these AGEs to cells and let them (Receptor for AGEs). As a consequence, the tissues are destroyed by a variety of damaging (Pennacchi et al., 2015).

AGEs are present in most tissues with in the body and their amounts rises from the age of twenty to onward. Though, other drugs or supplements and nutrients includes carnosine

proves very helpful to stop this process. Unluckily, the method of glycation not only disturbs proteins molecule, but also affects DNA molecules. A cross linked molecule of DNA is of no consume. Many medicines being explored which can in fact disrupt this bond between cross linked proteins which are glycated (Vaiserman & Lushchak, 2017).

5.3 Methylation

When different components of protein molecules, DNA and other molecules are attached to methyl groups to retain in active and good condition, it is known as methylation. This is required for appropriate tissue maintenance and is normally maintained at healthy levels through the system (Vaiserman & Lushchak, 2017). When some portions of DNA are methylated, unnecessary genes are permanently replaced and the organism is protected from an uneven DNA partition. Methylation prevents aberrant DNA from being transferred on to subsequent progeny of cells as a result.

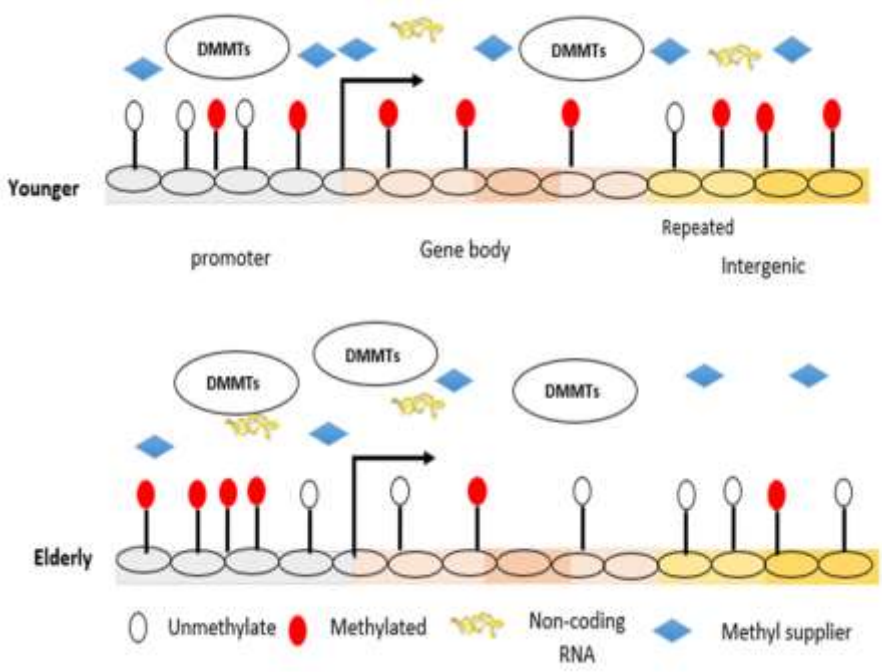

Figure.1: Schematic diagram of complex DNA methylation during aging **(**Xiao et al., 2019).

Moreover, hypermethylation in the site specific location during aging in the genome is also widely observed. Researchers have, for instance, found that in human aging hypermethylated regions lie ideally on bivalent chromatin domains and demonstrated that ribosomal DNA shows increasing methylation in elderly rats. Evidence has shown for now that global methylation reduction can be attributed to decreased DNA methyl transference (Dnmts) expression or inadequate supply in elderly people of folic acid. Any chronic inflammation procedure disturbs methylation because the immune system, which is severely involved to combat inflammation, gorges itself on methyl groups, leaving

nothing for other tissues of the body (Piskovatska et al., 2019). Low methylation is reflected by raising levels of homocysteine, which is present in chronic inflammatory methods such as lupus, diabetes and heart disease. More consumption of methylates lessens the threat of these disorders.

There are researchers who reflect that most changes related to age in the body are due to chronic infection. When there is prolonged inflammation, the tissues of the body are eaten by poisonous compounds causing diabetes, arthritis, and thickening of the arteries, hormonal imbalance, dementia and many others. Taking little dose of anti-inflammatory substances such as Aspirin retains inflammation related to age at bay. Hormones such as growth hormone, DHEA and melatonin must to be substituted or re-energized during aging to avoid the body from falling apart (Vaiserman & Lushchak, 2017). It is also quite important to ensure that the hormone binding active sites are in proper working order.

The future will include the use of stem cells (in embryonic and adults), to use manipulating genes and targeted supply of drugs and nutrients by means of nanotechnology to overcome the side effects.

VI. Chemotherapy or Anti-cancer drugs

Cancer is uncontrolled division of the cell due to mutation in any cancer signaling pathway (Kuczmarski et al., 2017). Any disturbance in the S phase, G phase and M phase of cell leads to formation of tumors neoplastic cells along with metastatic cancer (Lam et al., 2020). That's why it is necessary to understand cancer specific relative pathway and its blockage leads to stop persistence cancer progression. Chemotherapy drugs are generally classified as either reactive or interactive basis. The major classes of anticancer drugs are following alkylating agents, antimetabolites, natural product, antitumor antibiotics, miscellaneous drugs and hormonal therapy.

6.1 Alkylating Agents:

Alkylating agents are major anticancer drug which include nitro Soureas, alkyl sulfonates and nitrogen mustard (Wickström et al., 2017). Alkylating agents are cell cycle non-specific drugs their mode of action is very specific and unique because N7 position of guanine in DNA is alkylated by reactive molecular species generated by alkylating agents. Through this DNA strand break abnormal base pairing takes place along with cross-linking of bases. The major and important drugs involve in alkylating agents are cyclophosphamide, mechlorethanamine, platinum analogues, procarbazine and other alkylating agents like busulfan, carmustine and lomustine. These drugs are used in breast cancer, ovarian cancer, non-hodgkin lymphoma, chronic lymphocytic leukemia and neuroblastoma (Rothmiller et al., 2021). Its acute and chronic toxicity include nausea, vomiting myelosuppression and hemorrhagic cystitis.

6.2 Antimetabolites

Second major class of anticancer drugs is antimetabolites. They are structurally similar to endogenous compound and they are antagonist of purines, pyrimidine and Folic acid (Perez et al., 2019). They are cell cycle specific drugs which are responsible for cell cycle arrest through effecting and acting primarily on S phase. Their mechanism of action involve inhibition of dihydrofolate reductase because main motto is to decrease the synthesis of amino acid, thymidylate and purine nucleotides this will lead to defected protein metabolism (Maxwell et al., 2021). Other mechanism involves in his vision of those in which are responsible for the purine metabolism this can affect and harm proper functioning of DNA. The major drugs include in this class methotrexate, mercapto purine, thioguanine, fluorouracil, gemcitabine and cytarabine (Gonzales, 2019).

6.3 Antibiotics

Antibiotics are secondary metabolites made by micro-organisms or by higher plants and animals with anti-pathogens or other active substances that can interfere with developing of other living cells in the entire life course. Antibiotics can inhibit metastatic cancer and growth of cancer also promotes apoptosis according to research findings. For these factors, the use of antibiotics to help cure cancers is growing. Antibiotics are chemicals formed by anticancer microorganisms (Gao et al., 2020). The primary influence on unelected proliferation, violent growth and metastasis are the peptides and anthraquinones with clear and efficient inhibitors.

Anthracyclines, guanorycin, bleomycin, mitomycin, endiyne and actinomycin are primarily classified as antibiotic. The DNA and DNA-dependent RNA synthesis is inhibited and purine nucleosides can be selectively affected. DNA reconnection due to the topoisomerase causing the DNA to break up double-stranded, with the effects of cytotoxicity, daunorubicin and doxorubicin can both inhibit nuclear topoisomerases.

6.4 Natural products or vinca Alkaloids

Vinca alkaloids are cell cycle specific drugs and they are plant-derived drugs which includes vinblastine, vincristine, vinorelbine, etopside, teniposide, topetocan, irinotecan, paclitaxel and docetxel (Islam et al., 2019). Mechanism of action of vinca alkaloids include blockage of mitotic baluster by hindering the association of dimers of tubulin into the microtubules. M-phase of the cell division is affected by these chemotherapeutic drugs.

6.5 Miscellaneous drugs

Other class of drug is antitumor antibiotics they are design in such a way that they are dissimilar to microbial products and include anthracyclines, bleomycin and mitomycin. Their mechanisms of action in war generation of oxygen free radicals which bind to DNA and causes breakage of DNA. Other miscellaneous drugs are tyrosine kinase inhibitor with include imatinib (Jiao et al., 2018). The way of action of imatinib is inhibition of tyrosine kinase. Growth factor receptor inhibitor includes trastuzumab, the mode of action of this drug involved inhibition of binding of growth hormone to HER-2 growth receptor. The mode of action of this drug involves hindrance or blockage of growth hormone with receptor site so tumor vascularization inhibition takes place (Nogova et al., 2017).

VII. Personalized medicine

Personalized medicine (PM) is capable of making the therapy precise including best response from patient and with safety insurance. Personalized medicine approach offers a chance to produce agents that are targeted to a group of patients that are less responsive toward a specific medicine as expected and for those patients that are unable to cope with disease on the basis of classical treatment approaches. More successful consequences with less toxic effects achieved by selection of treatment by taking into account the genetic profile of individual patient. PM now combat the scenario of one size fit all model, with more precise and effective approach (Abrahams and Silver, 2010).

7.1 Basis of personalized medicine approach

The development of novel tools to explore the genome of human quickly and exactly.

1. Large-scale studies and sampling from a no. of patient help link genetic variations to diseases worldwide.
2. Health information technology (HIT) that raises the combination of research and clinical data leads to the PM.

Contemporary improvements in PM based on technology that approves a patient's genomics, proteomics, transcriptomics and metabolomics, which eventually cause approving disease. For example, genome sequencing can expose DNA mutation that effect different diseases. RNA-sequencing also showed which RNA molecules is cause of respective diseases. The fact about RNA is, it is changing within different atmospheric and environmental conditions, and so, its sequencing successfully leads to understanding of disease cause. Personalized medicine approach based on tools to analyses health risks and to design personalized health plans to benefit patients with reducing its risks, prevent disease and to cure it with tailored drugs with more precise methods (Jain, 2016).

VIII. Toxicity and side effects of Drugs

Toxicity is the extent to which a certain mixture of substances or a chemical substance can harm an organism. The effect can be on the entire organism, for example, the animal, bacteria, plants, or the effect on an organism's substructure, for example an organ like a liver or a cell. It can be referred to Toxicolog if it is related to study of the negative effects on living organisms of chemicals or any physical agents. Toxic can be a systemic toxin is one that affects a specific organ or whole organisms rather than a specific site. It is also can be an organ toxin is one that only affects particular organs or tissue. In many forms harmful effects can occur, problem can lead from instant death to gradual effects until months or years even. They can happen at different levels in the body, including a specific cell type, an organ, or a biochemical one. Awareness of the damage caused by toxic agents in the body due to medical knowledge has come a long way. Various changes in anatomy and body functions can now be seen as the consequence of previously unknown variations in specific biochemical in the body. Resistance of antibiotics can be due to spontaneous mutation happen as cells replicate and acquired resistance or due to gene transfer or transferred resistance conjugation (Etebu & Arikekpar, 2016).

8.1 Biochemical aspects of drug resistance

Drug conflict is the capability of microorganisms, such as viruses, bacteria, fungi or parasites, to produce in the company of a biochemical (drug) that would generally destroy it or limit its progression. It is the decrease in efficiency of a medicine in preserving a condition or disease. Drug resistance or anti-microbial resistance (AMR), improves when microorganisms, including viruses, bacteria, fungi and parasites, no longer respond to a drug that previously treated them effectively. AMR can lead to the following concerns: some contaminations being stiffer to

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Alkylating agents are major anticancer drug which include nitro Soureas, alkyl sulfonates and nitrogen mustard (Wickström et al., 2017). Alkylating agents are cell cycle non-specific drugs their mode of action is very specific and unique because N7 position of guanine in DNA is alkylated by reactive molecular species generated by alkylating agents. Through this DNA strand break abnormal base pairing takes place along with cross-linking of bases. The major and important drugs involve in alkylating agents are cyclophosphamide, mechlorethanamine, platinum analogues, procarbazine and other alkylating agents like busulfan, carmustine and lomustine. These drugs are used in breast cancer, ovarian cancer, non-hodgkin lymphoma, chronic lymphocytic leukemia and neuroblastoma (Rothmiller et al., 2021). Its acute and chronic toxicity include nausea, vomiting myelosuppression and hemorrhagic cystitis.

6.2 Antimetabolites

Second major class of anticancer drugs is antimetabolites. They are structurally similar to endogenous compound and they are antagonist of purines, pyrimidine and Folic acid (Perez et al., 2019). They are cell cycle specific drugs which are responsible for cell cycle arrest through effecting and acting primarily on S phase. Their mechanism of action involve inhibition of dihydrofolate reductase because main motto is to decrease the synthesis of amino acid, thymidylate and purine nucleotides this will lead to defected protein metabolism (Maxwell et al., 2021). Other mechanism involves in his vision of those in which are responsible for the purine metabolism this can affect and harm proper functioning of DNA. The major drugs include in this class methotrexate, mercapto purine, thioguanine, fluorouracil, gemcitabine and cytarabine (Gonzales, 2019).

6.3 Antibiotics

Antibiotics are secondary metabolites made by micro-organisms or by higher plants and animals with anti-pathogens or other active substances that can interfere with developing of other living cells in the entire life course. Antibiotics can inhibit metastatic cancer and growth of cancer also promotes apoptosis according to research findings. For these factors, the use of antibiotics to help cure cancers is growing. Antibiotics are chemicals formed by anticancer microorganisms (Gao et al., 2020). The primary influence on unelected proliferation, violent growth and metastasis are the peptides and anthraquinones with clear and efficient inhibitors.

Anthracyclines, guanorycin, bleomycin, mitomycin, endiyne and actinomycin are primarily classified as antibiotic. The DNA and DNA-dependent RNA synthesis is inhibited and purine nucleosides can be selectively affected. DNA reconnection due to the topoisomerase causing the DNA to break up double-stranded, with the effects of cytotoxicity, daunorubicin and doxorubicin can both inhibit nuclear topoisomerases.

6.4 Natural products or vinca Alkaloids

Vinca alkaloids are cell cycle specific drugs and they are plant-derived drugs which includes vinblastine, vincristine, vinorelbine, etopside, teniposide, topetocan, irinotecan, paclitaxel and docetxel (Islam et al., 2019). Mechanism of action of vinca alkaloids include blockage of mitotic baluster by hindering the association of dimers of tubulin into the microtubules. M-phase of the cell division is affected by these chemotherapeutic drugs.

6.5 Miscellaneous drugs

Other class of drug is antitumor antibiotics they are design in such a way that they are dissimilar to microbial products and include anthracyclines, bleomycin and mitomycin. Their mechanisms of action in war generation of oxygen free radicals which bind to DNA and causes breakage of DNA. Other miscellaneous drugs are tyrosine kinase inhibitor with include imatinib (Jiao et al., 2018). The way of action of imatinib is inhibition of tyrosine kinase. Growth factor receptor inhibitor includes trastuzumab, the mode of action of this drug involved inhibition of binding of growth hormone to HER-2 growth receptor. The mode of action of this drug involves hindrance or blockage of growth hormone with receptor site so tumor vascularization inhibition takes place (Nogova et al., 2017).

VII. Personalized medicine

Personalized medicine (PM) is capable of making the therapy precise including best response from patient and with safety insurance. Personalized medicine approach offers a chance to produce agents that are targeted to a group of patients that are less responsive toward a specific medicine as expected and for those patients that are unable to cope with disease on the basis of classical treatment approaches. More successful consequences with less toxic effects achieved by selection of treatment by taking into account the genetic profile of individual patient. PM now combat the scenario of one size fit all model, with more precise and effective approach (Abrahams and Silver, 2010).

7.1 Basis of personalized medicine approach

The development of novel tools to explore the genome of human quickly and exactly.

3. Large-scale studies and sampling from a no. of patient help link genetic variations to diseases worldwide.
4. Health information technology (HIT) that raises the combination of research and clinical data leads to the PM.

Contemporary improvements in PM based on technology that approves a patient's genomics, proteomics, transcriptomics and metabolomics, which eventually cause approving disease. For example, genome sequencing can expose DNA mutation that effect different diseases. RNA-sequencing also showed which RNA molecules is cause of respective diseases. The fact about RNA is, it is changing within different atmospheric and environmental conditions, and so, its sequencing successfully leads to understanding of disease cause. Personalized medicine approach based on tools to analyses health risks and to design personalized health plans to benefit patients with reducing its risks, prevent disease and to cure it with tailored drugs with more precise methods (Jain, 2016).

VIII. Toxicity and side effects of Drugs

Toxicity is the extent to which a certain mixture of substances or a chemical substance can harm an organism. The effect can be on the entire organism, for example, the animal, bacteria, plants, or the effect on an organism's substructure, for example an organ like a liver or a cell. It can be referred to Toxicolog if it is related to study of the negative effects on living organisms of chemicals or any physical agents. Toxic can be a systemic toxin is one that affects a specific organ or whole organisms rather than a specific site. It is also can be an organ toxin is one that only affects particular organs or tissue. In many forms harmful effects can occur, problem can lead from instant death to gradual effects until months or years even. They can happen at different levels in the body, including a specific cell type, an organ, or a biochemical one. Awareness of the

damage caused by toxic agents in the body due to medical knowledge has come a long way. Various changes in anatomy and body functions can now be seen as the consequence of previously unknown variations in specific biochemical in the body. Resistance of antibiotics can be due to spontaneous mutation happen as cells replicate and acquired resistance or due to gene transfer or transferred resistance conjugation (Etebu & Arikekpar, 2016).

8.1 Biochemical aspects of drug resistance

Drug conflict is the capability of microorganisms, such as viruses, bacteria, fungi or parasites, to produce in the company of a biochemical (drug) that would generally destroy it or limit its progression. It is the decrease in efficiency of a medicine in preserving a condition or disease. Drug resistance or anti-microbial resistance (AMR), improves when microorganisms, containing viruses, fungi, parasites and bacteria, no longer react to a medicine that formerly preserved them efficiently. Anti-microbial resistance can lead to the subsequent concerns: certain contaminations existence stiffer to governor and the remaining longer intimate the body (Matlashewski et al., 2017). Anti-microbial Resistance (AMR) ensues when viruses, bacteria, fungi or parasites, change over interval and no longer react to drugs making impurities stiffer to indulgence and accumulative the danger of infection spread, severe illness and finally death.

8.2 Mechanisms of Antibiotic Resistance

Resistance to one anti-microbial class can typically be attained over several biochemical ways, and one microbial cell might be accomplished of consuming a squad of apparatuses of confrontation to endure the influence of an antibiotic (Berman & Krysan, 2020). Consequently, the infectious cell reins the entrance of these particles to periplasmic interstellar, permitting the manufacture of β-lactamases in adequate absorptions toward slant the kinetics in courtesy of devastation of the antibiotic particle. Equally, this "compartmentalization" improvement is lacking in Gram positive bacteria, while creation of β-lactamases too looks to be positive in assured circumstances (e.g., staphylococcal penicillinase). To deliver an inclusive organization of the resistance mechanisms of antibiotic, so we will classify them permitting to a chemical way elaborate in resistance, as follows:

1. Anti-microbial molecule variations
2. Inhibition of the multiple accomplishment the antibiotic object (by reducing infiltration or dynamically extruding the anti-microbial compound),
3. Alterations to and/or by fleeting of objective sites
4. Confrontation due to universal cell-adaptive procedures

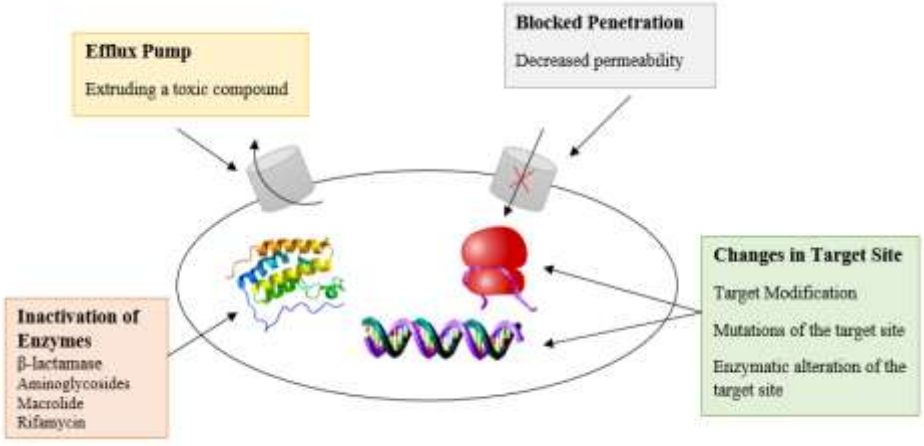

Figure.2: Resistance mechanism of antibiotic

8.3 Modifications of the drug

Modifications of the drug is the most effective microbial approaches to manage with existence of medicine is to crop the enzymes that deactivate the medicine by accumulation exact biochemical moieties to the compound or that terminate the molecules themself, interpretation the antibiotic impotent to cooperate with its object (Cowen et al., 2015).

8.4 Reduced permeability

There are several medicine used in medical practice, which have intracellular microbial objects or, in the situation of Gram-negative bacteria, objectives sited in the cytoplasmic membrane. Consequently, the molecule essential infiltrate the exterior and the membrane of cytoplasm to apply its anti-microbial effect (Das, 2020). Microorganisms have advanced procedures to avoid the antibiotic drugs from accomplishment its intracellular object by reducing the commitment of anti-microbial compound. Reduced permeability mechanism is mostly significant in the Gram-negative bacteria (for the intention quantified above), regulating the invasion of ingredients from outside environment. Actually the outside membrane turns the main line of protection against the infiltration of various deadly complexes, containing numerous anti-microbial agents. Hydrophilic particles such as tetracyclines, β-lactams, and certain fluoroquinolones are mainly precious through modifications now absorptivity of external membrane meanwhile they frequently consumption water-filled diffusion stations identified as porins to irritate this obstacle (Matsson et al., 2016).

8.5 Efflux pumps

The invention of compound bacteriological machineries accomplished of extruding a deadly molecule out of cell can too consequence in anti-microbial confrontation. The narrative of an efflux pumps system capable to drive tetracycline out of the E. coli cytoplasm, dates since the 1980s and it was the first compound to be designated. Later then, several programmers of efflux system have been categorized in both Gram-positive bacteria and Gram-negative bacteria (Schindler et al., 2016). This process of confrontation disturbs a widespread variety of ant-microbial modules comprising polymyxins, protein separation inhibitors, β-lactams, fluoroquinolones, and carbapenems. The genes programming efflux pumps system can be sited in MGEs (as primarily labelled for the tet gene) or in the chromosome.

8.6 Modifications in Target Sites

A mutual scheme aimed at microbes toward improve anti-microbial conflict to evade exploit of antibiotic via intrusive with their objective spot. To attain this, microbes have progressed altered strategies, containing defense of the objective (evading the medicine from accomplishment its obligatory spot) and alterations of objective site that consequence in reduced attraction for the molecule of antibiotic(Smorodinsky-Atias et al., 2020). Objective safety while certain genetic cause's encoding for the proteins that facilitate objective safety have been originate in chromosome of bacterial cell, best of the clinically related inheritable factor elaborate in this process of confrontation are approved by MGEs. Examples of medicines exaggerated by this mechanism comprise tetracycline (Tet[M], fluoroquinolones (Qnr) and fusidic acid (FusB and FusC).

8.6.1 Alteration of the target site

Presenting alterations to the objective site is the best procedure of medication confrontation in bacteriological pathogens disturbing practically all relations of antimicrobial combinations. These objective variations might be comprised of:

1. The point mutations in the genetic factor encrypting the objective site,
2. enzymatic modifications of the obligatory spot (for example adding of methyl groups)
3. Additional / sidestep of the inventive object.

As revealed, irrespective of the kind of variation, the ultimate result is constantly similar, a reduction in the attraction of the antibiotic for the objective site (Berman & Krysan, 2020).

Conventional illustrations of all of these tactics will be exhaustive further down.

8.6.2 Mutations of the objective site

The best example of mutational confrontation is the expansion of rifampin confrontation. Rifampin is rifamycin that wedges bacterial transcript by preventing the DNA-dependent RNA polymerase, which is a multifaceted enzyme with a structure of $\alpha 2\beta\beta'\sigma$ subunit (Vedithi et al., 2018). The rifampin obligatory compact is an extremely preserved structure situated in the beta subunit of the RNA polymerase (encoded by rpoB), and after obligatory, the antibiotic molecule interjects record by directly hindering the path of the nascent RNA. Complex rifampin confrontation has been exposed to transpire by single-step point mutations subsequent in amino acid substitutions in the rpoB gene, and several diverse genetic modifications have been described.

8.6.3 Enzymatic alteration of the objective site

The methylation of the ribosome catalyzed by an enzyme resolute by the erm genetic factor, which effects in macrolide confrontation is the best examples of confrontation over enzymatic change of the objective spot (Schroeder & Stephens, 2016). Due to this chemical alteration, the required of the anti-microbial particle to its objective is reduced. Subsequently the macrolides, streptogramin B and lincosamides, antibiotics have covering required positions in the 23S subunit of rRNA, manifestation of the erm genetic factor converses cross-resistance to all associates of the MLSB group. More than 30 erm genes have been designated, several of them situated in MGEs, which can excuse for their sufficient circulation amongst different genera, containing both aerobic and anaerobic Gram-negative bacteria and Gram positive bacteria.

8.7 Resistance Due to Global Cell Adaptations

Over years of evolution, microorganisms especially bacteria have advanced cultured procedures to manage with ecological pressures and stressors in instruction to persist in the utmost hostile surroundings, containing the human body. Bacteria want to contend for nutrients and evade the outbreak of molecules formed by conflicting entities to increase the "upper hand." Exclusive a precise host, bacterial organisms are frequently criticized by the host's immune system, and to create themselves in specific biological places, it is critical that they acclimate and survive with these hectic conditions (Mansoori et al., 2017). Therefore, bacteriological pathogens have developed very difficult mechanisms to evade the interruption of essential cellular procedures such as cell wall creation and membrane homeostasis. Improvement of confrontation to vancomycin and daptomycin (DAP) (low-level in S. aureus) are the supreme clinically related examples of conflict phenotypes that are the outcome of a global cell-adaptive reaction to the antiseptic outbreak.

Table 1: Mechanisms of Acquired Drug Resistance (Peterson & Kaur, 2018).

Mechanism	**Antimicrobial Agent**	**Drug Action**	**Mechanism of Resistance**
Destroy drug	Chloramphenicol Beta-lactam antibiotics (cephalosporin and penicillin) Aminoglycosides	deterring protein synthesis by binds to 30S Ribosomal subunit deterring peptidoglycan synthesis by binds to penicillin-binding proteins, deterring development of peptide bonds by bind to 50S ribosomal subunit	Plasmid encrypt enzymes that chemically change the medicine (e.g., by phosphorylation and acetylation), so deactivating it. Plasmid encrypts beta-lactamase, which exposed the beta-lactam loop, deactivating it. Plasmid encrypts an enzyme that acetylates the medicine, so deactivating it.
Modifies drug target	Aminoglycosides Beta-lactam antibiotics (cephalosporin and penicillin) Rifampin Erythromycin Trimethoprim Quinolones	deterring protein synthesis by binds to 30S ribosomal subunit, Deterring peptidoglycan synthesis by binds to penicillin-binding proteins, deterring protein synthesis by bind to 50S ribosomal subunit Also binds to DNA topoisomerase which is an enzyme important for DNA synthesis deterring start of RNA synthesis by binds to the RNA polymerase enzyme Obstruct the enzyme dihydrofolate decreases, hindering the folic acid path	Microorganisms (bacteria) make a different 30S ribosomal subunit that does not bind to the drug Microorganisms (bacteria) mark improved penicillin-binding proteins that do not bind to the medicine. Microorganisms (bacteria) make an arrangement of 50S ribosomal subunit that does not binds to the medicine. Microorganisms (bacteria) make an improved DNA topoisomerase that does not binds to the medicine. Microorganisms (bacteria) make a changed polymerase that does not bind to the medicine. Microorganisms (bacteria) make an improved enzyme that does not binds to the medicine.

Prevents drug entrance or eliminates drug	Erythromycin Tetracycline Penicillin	Deterring peptidoglycan synthesis by binds to penicillin-binding proteins deterring protein production by bind to 50S ribosomal subunit deterring protein synthesis by hindering tRNA by binds to 30S Ribosomal subunit	Microorganisms (bacteria) altered the shape of the outside of membrane porin proteins, avoiding drug from arriving cell. New membrane transportation system stops medicine from arriving cell. New membrane transportation system drives medicine out of cell.

IX. Other side effects of drugs

9.1 Allergy

Allergic medicine response is a confrontational drug reaction that marks from a precise immunologic reaction to a medication (Marchant, 2018). The different allergies caused by different antibiotics are as following,

- ⇒ **Pruritus** (unpleasant sensation of the skin)
- ⇒ **Flushing** (temporary reddening of the skin)
- ⇒ **Urticaria** (Inflammation due to histamine)
- ⇒ **Angioedema** (swelling of mucous membranes)
- ⇒ **Bronchospasm** (abnormal contraction of the smooth muscle)
- ⇒ **Abdominal** distress (between the chest and pelvic regions)
- ⇒ **Hypotension** (define low blood pressure as 90/60 mm Hg or below)

9.2 Side Effects of Antibiotics

Antibiotics cause many side effects besides the enormous benefits. These include the alteration of the normal flora in intestine necessary for contraceptive abs. It also increases or inhibits CYP enzymes in liver changing plasma conc. of drugs like Warfarin, digoxin, theophylline. It also interacts with body plasma protein binding.

9.3 Suppression of Normal Flora:

What is Normal flora?

Microbes that living on or in human bodies, and generally do not cause human diseases. Normal flora play's different physiological role in body like antagonism acts as colonization resistance of exogenous pathogenic microbes (Klaassen & Cui, 2015). Trophism; normal flora in the intestinal tract synthesizes nutrients that can be absorbed. Immunoenhancement; normal flora promotes the development of local lymphatic tissues. Due to drug over usage the normal flora alters in intestine necessary for contraceptive abs. It also increases or inhibits CYP enzymes in liver.

9.3 Environmental Hazards

Antibiotic resistance gene pollution can increase the chances of gaining resistance of human pathogens. The release of human microbiota residues into environments with bacteria that are enriched with resistance elements makes it possible for bacteria that have a human connection to obtain new resistance determinants. For these reasons, the release of human commensal and resistant or susceptible infectious bacteria residues from hospitals as well as antibiotics should be reduced to the minimum to prevent genetic material exchanges (Hauser, 2020).

X. Conclusion

A pharmaceutical drug is a chemical compound that binds to proteins in the body to trigger a biological process. Pharmacodynamics includes the physiological and biochemical drugs effects and their mechanisms of action within or on the body of parasites and micro-organisms. Different medicines are used to cure, prevent and combat different diseases by affecting the physiological functions. An association between two or more drugs that makes the overall effect of each drug greater than the amount of each drug's individual effects. Along with its benefits, there are side effects that are appeared by overusage or repetitive use age of drug. Resistance of antibiotics can be due to spontaneous mutation happen as cells replicate and acquired resistance or due to gene transfer or transferred resistance conjugation. The imminent will contain influencing

genes, accumulative consumption of stem cells (developing and mature) and embattled transport of nutrients and medicines exhausting nanotechnology. It is my expectation that this will help you activate your educational expedition in pharmacological fields.

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